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A Stereoselective Synthesis of Dinucleotide Boranophosphate, Using Chiral Indole-oxazaphosphorine Intermediates

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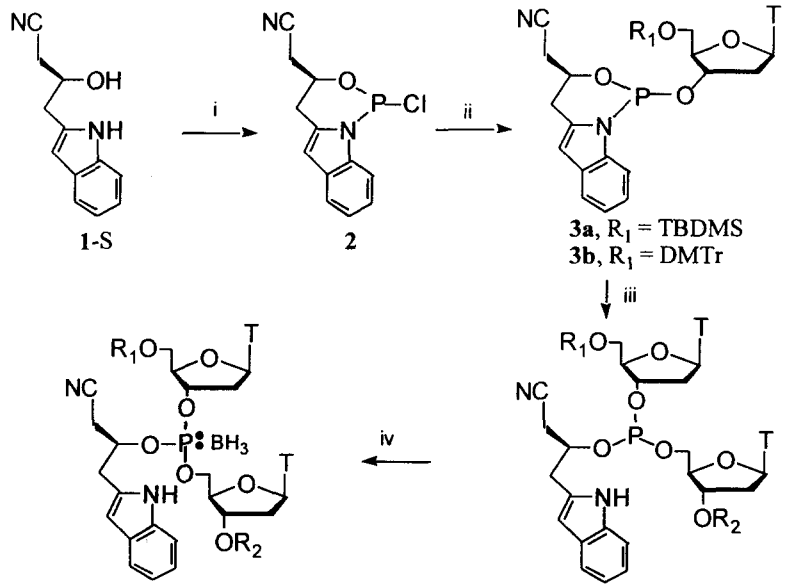
Abstract: A stereoselective synthesis of a Sp dinucleotide boranophosphate with a de of > 98%, using (S)-3-hydroxyl-4-(2-indolyl)butyronitrile as chiral auxiliary, is reported. The conversion of phosphite triester to boranophosphate with BH_3-Me_2S proceeds with retention of configuration at the phosphorus atom. The procedure may be adaptable to solid phase synthesis.

In the preceding article,[1] we reported the synthesis of the Sp and Rp diastereomers of dithymidine boranophosphate. It has also been known that using chiral auxiliary **1** can lead to stereoselective synthesis of chiral phosphorothioate (de > 97%).[2] We therefore investigated the use of chiral auxiliary **1** in the synthesis of chiral boranophosphates.

SCHEME 1



1-S **2**

3a, R_1 = TBDMS
3b, R_1 = DMTr

5a, R_1 = TBDMS, R_2 = TBDPS
5b, R_1 = DMTr, R_2 = DMTr

4a, R_1 = TBDMS, R_2 = TBDPS
4b, R_1 = DMTr, R_2 = DMTr

i. PCl_3, Et_3N/THF, 0 ^{0}C; ii. T_3OH/THF, 0 ^{0}C; iii. T_5OH, DBU/THF, RT; iv. BH_3-Me_2S in 2.0 M THF

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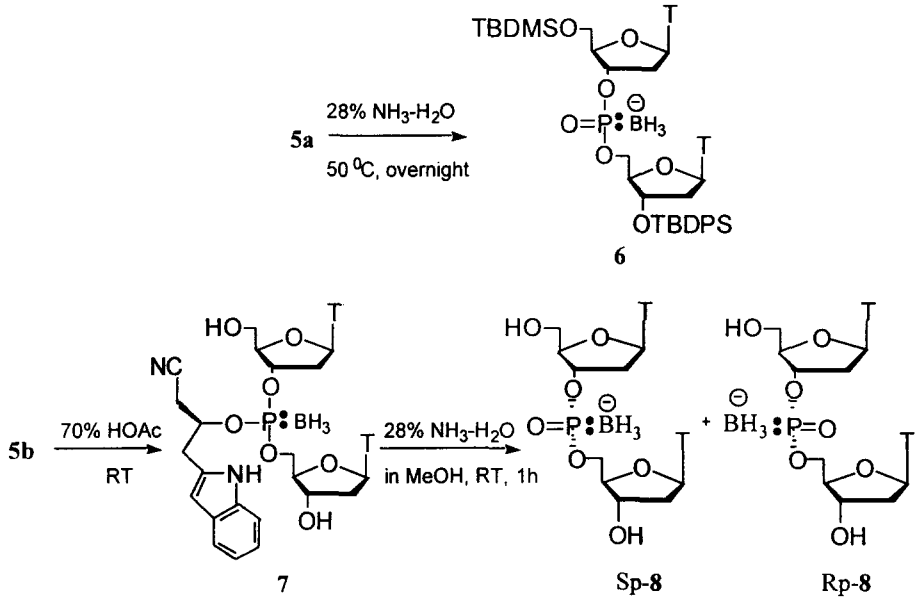
As reported, [2] the chiral auxiliary **1**-(S) can be synthesized from (R)-glycidol in 5 steps. In THF, the reaction of **1**-(S) with PCl_3 was complete in several minutes to give phosphorochloridite **2** at 0 °C; 5'-O-TBDMS-thymidine (**T_3,OH**) was then added at 0 °C to provide the indole-oxazaphosphorine **3a** consisting of two diastereomers in a ratio of 8 : 1 - 12 : 1. When 3 eq. of **3a** was treated with 1 eq. of 3'-O-TBDPS-thymidine (**T_5,OH**), only one isomer **4a** (^{31}P NMR showed a single peak at 141.61 ppm) was obtained. After reaction with dimethyl sulfide - borane (BH_3-Me_2S) (Scheme 1), the phosphite peak disappeared within 5 - 10 min to give a broad peak at 116.83 ppm for boranophosphate **5a**. The diastereomeric ratio could not be determined from ^{31}P NMR spectrum because of peak broading. We therefore tried to get unprotected dinucleoside boranophosphate **8**. The chiral auxiliary was easily removed with 28% NH_3-H_2O at 50 °C overnight to form **6** (^{31}P NMR 96.53 ppm, broad). The deprotection of the silyl groups on **6** with TBAF or TBAF/HOAc/THF provided the boranophosphate **8** (^{31}P NMR ~93 ppm, broad) in low yield and another product showed a single peak at ~29 ppm in the ^{31}P NMR spectrum. The by-product has no BH_3 moiety since no peak was observed in the ^{11}B NMR spectrum (Scheme 2).

SCHEME 2



In order to improve the yield of dinucleoside boranophosphate **8** and avoid the loss of the BH_3 moiety which was probably due to reaction with fluoride ion, we repeated the reaction of phosphorochloridite **2** with 5'-O-dimethoxytritylated **T_3,OH**. The indole-oxazaphosphorine **3b** was obtained in a diastereomeric ratio of 16 : 1. After adding 3'-O-dimethoxytritylated **T_5,OH**, phosphite triester **4b** was obtained. The reaction of **4b** with BH_3-Me_2S in 2.0 M THF gave boranophosphate **5b** (^{31}P NMR: 117.06 ppm, broad). Interestingly, the DMTr groups on **5b** were not removed in the boronation step even though the reaction was allowed to proceed overnight at RT.[1] Reaction with 70% HOAc removed the DMTr groups and gave **7**, which was

converted to final compound **8** by using 28% NH_3-H_2O in methanol at RT for 1 h. In the coupling step, when 1 eq. of **3b** and 1 eq. of **T_5-OH** was used, 10 : 1 of two diastereomers of phosphite triester **4b** (^{31}P NMR: 140.95 : 140.86 ppm = 10 : 1) was obtained. After removing chiral auxiliary, boranophosphates Sp-**8** and Rp-**8** was obtained in the same diastereomeric ratio of 10 : 1 as for **4b**. When 3 eq. of **3b** and 1 eq. of **T_5-OH** were used, the coupling reaction provided only one diastereomer of phosphite triester **4b** (^{31}P NMR: 140.96 ppm) which was transformed to only one diastereomer of Sp-**8**. The diastereomeric ratio of **8** could not be obtained from ^{31}P NMR spectrum because of a broad peak at ~ 93 ppm. However, it can be obtained from ^{1}H NMR with comparison with the data in the literature[1,3] (Figure 1). Also, the absolute configuration at phosphorus in Sp-**8** and Rp-**8** was assigned by ^{1}H NMR comparison with literature data.[1, 3]

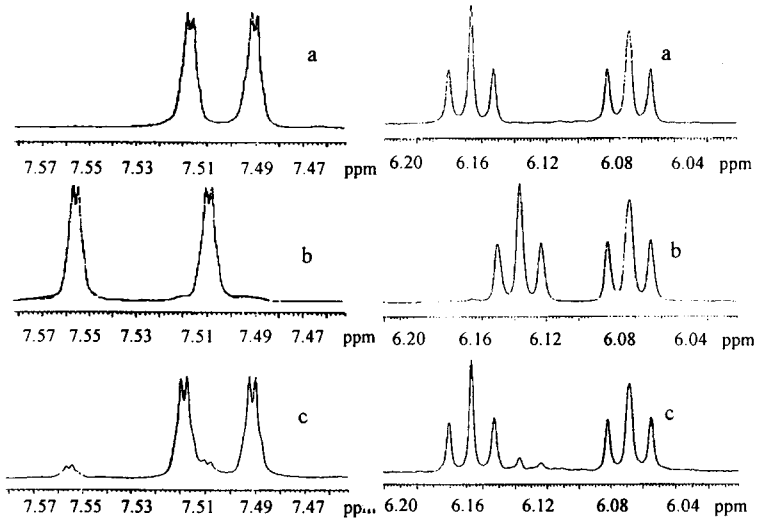


Figure 1: Part of ^{1}H NMR Spectra of Sp-**8** (a), Rp-**8** (b)[1] and a diastereomer mixture of Sp-**8** and Rp-**8** (10 : 1) (c) in D_2O. Left spectra: assigned to ^{5}H-6 and ^{3}H-6, Right spectra: assigned to ^{5}H-1' and ^{3}H-1'.

It is known that the Rp - dithymidine phosphorothioate can be synthesized from chiral auxiliay **1**-(S)[2] and that the conversion of phosphite triester to phosphorothioate proceeds with retention of stereochemistry.[4] Since Sp dithymidine boranophosphate was obtained from **1**-(S), it was concluded that the conversion of phosphite triester to boranophosphate by dimethyl sulfide - borane took place with retention of configuration. Noting that sulfur is the largest atom around the phosphorus center in a nucleotide phosphorothioate while boron is the smallest atom around the phosphorus center in a nucleotide boranophosphate, a Rp configuration in phosphorothioate corresponds to an Sp configuration in boranophosphate.

It should be possible to get pure Rp dithymidine boranophosphate from chiral auxiliary **1**-(R), since the Sp dithymidine phosphorothioate can be obtained from chiral auxiliary **1**-(R).[2] The method reported here might be adaptable to the solid phase synthesis of chiral oligonucleotide boranophosphates.

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